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Hypoxic ischemic brain injury following in hospital cardiac arrest – Lessons from autopsy

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ABSTRACT

Hypoxic ischemic brain injury (HIBI) is the most decisive factor in determining the outcome following a cardiac arrest. After an arrest, neuronal death may be early or delayed. The aim of our study is to determine the prevalence and predictors of HIBI on autopsy following an in hospital cardiac arrest. We retrospectively reviewed the medical records of patients who sustained an in hospital cardiorespiratory arrest and underwent autopsy following in hospital mortality at our tertiary care medical center from January 2004–June 2012. These patients were identified from the autopsy registry maintained by the Department of Pathology and were classified into two groups based on the presence or absence of HIBI on autopsy. We compared the baseline demographics, risk factors, total duration of cardiopulmonary resuscitation, number of resuscitative events and survival time between both groups. Multivariate logistic regression analysis was performed to identify predictors of hypoxic ischemic injury following cardiac arrest. Out of 71 patients identified during this study period, 21% had evidence of HIBI on autopsy. On univariate analysis, predictors of HIBI were prolonged hospital stay, prolonged survival time following an arrest and a slight increased trend following multiple resuscitative events. On multivariate analysis, prolonged survival time was the only significant predictor of HIBI. Similar to other prognostication cardiac arrest studies, there were minimal predictors of early neuronal injury even on autopsy.

1. Introduction

Hypoxic-ischemic brain injury (HIBI) is the most feared complication of a cardiac arrest. Despite major advances, it carries a significant mortality with a survival rate of 10% for out-of-hospital cardiac arrest.[1] A mixture of cardiac and pulmonary pathologies result in impairment of tissue perfusion and oxygenation eventually leading to a cardiopulmonary arrest.[2]

Following cardiac arrest, brain damage occurs within minutes or after prolonged duration depending upon the animal model and conditions that accompany them.[3–5] There is minimal evidence of pathological brain damage in the initial few hours, which progressively increases with time.[6,7] Factors including duration of circulatory arrest,[8] survival time following cardiac arrest,[6] hypoperfusion before and after cardiac arrest[3] and selective neuronal vulnerability[9–11] play significant roles in the degree of pathological manifestations. There is a great variability in reliability from circumstances during cardiopulmonary resuscitation in prediction of outcomes.[12]

Currently, there is limited data on predictors of early neuronal death on autopsy in humans following an in hospital cardiac arrest. Since mortality is the most feared outcome of HIBI, identifying these predictors may hopefully help us not only predict which patients are at risk, but also to guide us in prevention. The aim of our study is to determine the prevalence and predictors of HIBI on autopsy following an in hospital cardiac arrest.

2. Materials and methods

2.1. Study population

We retrospectively reviewed the medical records and autopsy reports of all patients who suffered from a cardiorespiratory arrest during their hospitalization and underwent autopsy following in hospital mortality at our tertiary care center. These patients were

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identified from the autopsy registry maintained by the Department of Pathology. All patients of age 18 years and above who met the above criteria from January 2004–June 2012 were included. Patients with out-of-hospital cardiac arrest were excluded. We dichotomized our patients into two groups based on the presence or absence of HIBI on autopsy findings. The pathologic criteria used to determine hypoxic ischemic brain injury has been previously described.[13,14] We reviewed the demographics, risk factors, duration of cardiopulmonary resuscitation (CPR), number of resuscitative events, death to autopsy time, initial cardiac rhythm, length of hospital stay and autopsy findings. If multiple resuscitative events were performed, the cumulative time of individual events was used as the duration of CPR. Survival time was defined as duration from return of spontaneous circulation (ROSC) to death. All autopsies were performed within 30 h of death. The specimens were fixed in formalin prior to pathological evaluation.

2.2. Statistical analysis

For statistical analysis, we compared two groups of patients (patients with and without HIBI) using Chi-Square test or Fisher's exact test for categorical variables and Wilcoxon Rank Sum test or *t*-test for continuous variables. A multivariate logistic regression analysis was performed to identify predictors of hypoxic ischemic brain injury. Variables with statistical significance in univariate analysis were included in the multivariate analysis. Multiple code variables were included in the multivariate model as it was thought to be clinically relevant and it showed trend for statistical significance. Statistical significance was defined as p value ≤ 0.05. For statistical analysis we used JMP (John's Macintosh Program) 10th edition software.[15]

3. Results

Out of 543 autopsies performed during this study period, we identified 71 patients who had at least one episode of cardiopulmonary arrest that required resuscitation during their hospitalization. Among these 71 patients, pathological evidence of hypoxic brain damage was identified in 21% (15 patients) on autopsy. These included identification of eosinophilic cytoplasm, pyknotic nuclei, shrinkage, degeneration, loss, vacuolization of the neurons and swelling of axons (spheroids). Baseline co-morbidities of both the groups were comparable (Table 1). Although diabetes was twice as common in HIBI cohort (40% in HIBI verses 20% in no HIBI cohort, $p = 0.12$) it was not statistically significant. Prolonged hospital stay (19 ± 26 verses 8 ± 11, $p = 0.018$), prolonged survival time (93 ± 236 verses 15 ± 74, $p = 0.035$) and a survival time of 2 h or more following an arrest (67% verses 18% $p \leq 0.001$) were more common in the HIBI group compared to the group without HIBI. There was a tendency towards HIBI with multiple resuscitative events (40% verses 16%, $p = 0.056$) although this did not reach statistical significance. On multivariate analysis (Table 2), only a survival time of 2 h or more following ROSC was the only identifiable predictor of hypoxic brain damage on autopsy (OR 10.7, 95% CI: 1.9–70.1; $p \leq 0.01$).

Table 1
Predictors of HIBI on autopsy.

	HIBI ($n = 15$)	No HIBI ($n = 56$)	*P*-value
Age (years, mean ± SD)	56 ± 18	52 ± 14	0.352
Gender (% males)	47%	48%	0.915
Race (Caucasian)	40%	60%	0.152
Hypertension (%)	67%	50%	0.250
Diabetes mellitus (%)	40%	20%	0.115
Hyperlipidemia (%)	13%	13%	0.932
Stroke (%)	7%	0%	0.211
Coronary artery disease (%)	7%	9%	1.000
Atrial fibrillation (%)	7%	7%	1.000
Smoking (%)	20%	16%	0.723
Alcohol (%)	7%	4%	0.515
Substance abuse (%)	0%	7%	0.572
Number of resuscitation events (>once %)	40%	16%	0.056
Code time (minutes, mean ± SD)	34 ± 22	35 ± 21	0.794
Survival time (minutes, mean ± SD)	93 ± 236	15 ± 74	0.035
Survival time more than 2 h (%)	67%	18%	<0.001
Death to autopsy time (hours, mean ± SD)	18 ± 8	20 ± 12	0.433
Code type (VT/VF %)	0.11%	0%	0.196
Length of hospital stay (days, mean ± SD)	19 ± 26	8 ± 11	0.018

VT = Ventricular tachycardia, VF = Ventricular fibrillation, SD = Standard deviation.

4. Discussion

HIBI is one of the most devastating consequences of cardiac arrest. About 80% of these are out-of-hospital cardiac arrest with a survival rate of 10%.[1] The survival rate of in hospital cardiac arrest varies from 2.4% to 18.1%.[16,17] Cardiac arrest results in a wide spectrum of catastrophic organ damage with death being the worst outcome.

Out of 71 patients who met our inclusion criteria, 21% had pathological evidence of HIBI on autopsy. Although on univariate analysis, major predictors of hypoxic ischemic brain injuries were prolonged hospital stay, prolonged survival time especially those who survived for 2 h or more after ROSC, but on multivariate analysis, only a survival time of 2 h or more after ROSC was the only identifiable predictor implying that sufficient time is required for pathological manifestations even in fatal conditions.

Preliminary data from a large multicenter double-blind randomized trial demonstrated that diabetes mellitus, arrest time (time from collapse to initiation of CPR) of more than 5 min, CPR more than 20 min and electrocardiographic patterns other than ventricular tachycardia and ventricular fibrillation[18] were independent predictors of poor outcome. But subsequent studies have shown a high false positive rate of these variables, ranging from 20 to 27%, suggestive of poor accuracy in predicting outcomes in these patients.[12] The results of our study further strengthen the poor reliability of these variables. There was a strong correlation between prolonged survival time and HIBI, which is consistent with a prior study.[6]

Animal models have revealed a significantly higher frequency of ischemic neurons following multiple, intermittent, brief cerebral insults when compared to a single ischemic event,[19] a trend which was noticed only on univariate analysis in our cohort. This finding should be interpreted with caution, as we were limited by a small sample size. In future, this finding will need to be confirmed in larger prospective studies. The majority of our patients were non-ventricular fibrillation rhythm, but this did not accelerate early neuronal damage.

Prior experiments have shown irreversible brain damage occurring 5 min after a circulatory arrest.[20] Following an ischemic event, cell death may occur as early as few hours or days later depending on the length of insult and cell population, with shorter delay from longer insults.[21] We did not find a correlation between the duration of CPR and pathological evidence of brain damage,

Table 2
Multivariate analysis of HIBI on autopsy.

	Odds ratio	95% CI	*P* value
Number of resuscitative events	0.59	0.08–3.54	0.57
Survival time more than 2 h	10.7	1.9–70.1	<0.01
Length of hospital stay	1.02	0.96–1.09	0.46

CI = confidence interval.

indicating that multiple factors like hypoxic preconditioning, pre-arrest cerebral function and neuronal damage, prior medications,[22] body temperature,[23] degree and duration of hypoperfusion before, during and after an arrest play a significant role in the outcome. Recent animal data has revealed a role of hypoxic preconditioning in attenuating ischemic brain injury following cardiac arrest, but this will need to be evaluated prospectively in humans.[24,25]

In humans, reduced numbers of Purkinje cells with lack of nuclear staining and fading out of cytoplasm have been identified among those resuscitated for at least 2 h[26] Earliest manifestations of ischemic neuronal necrosis were identified in cortical layers 3, 5 and 6 following 5 h of cardiac arrest.[6] In our study, hypoxic injury was global in 47%, affecting the hippocampus and frontal lobes in 33% each, followed by involvement of other regions.

Major drawbacks of our study include a small cohort, retrospective nature, a large selection bias that motivates an autopsy request, pathological data only, lack of arrest time prior to CPR although there is a short response time for in-hospital cardiac arrests, lack of perfusion and oxygenation status prior, during and after the arrest and lack of a control group. Additionally we analyzed only the dead; which represents the worst end of the disease spectrum.

5. Conclusion

In summary, cardiac arrest initiates a cascade of events, which evolves with time resulting in increased prevalence of pathological brain damage among those with prolonged survival time. Hypoxic brain injury results from a continuum of events that not only includes the arrest phase but also precedes and follows the arrest. Circumstances surrounding CPR did not accelerate the pathological evidence of hypoxic brain damage. There was a trend towards hypoxic brain injury among those who sustained multiple resuscitative events, but this will need to be evaluated in larger prospective trials.

The implementation of therapeutic hypothermia has significantly improved outcomes in patients with hypoxic ischemic injury.[27] Various neuroprotective agents have been identified in animal models and will need to be evaluated in humans.[28–30] Large measures need to be undertaken to identify early predictable biomarkers and treatment modalities targeting at different levels and various time frames in conjunction with hypothermia in order to improve survival and outcomes.

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Conflict of interest
None.

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